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FACTORS CONCERNED IN THE PRODUCTION OF MITOSIS IN ORGANISMS DISPLAYING CELL CONSTANCY.¹

H. J. VAN CLEAVE.

The condition of absolute identity in cellular structure found in individuals of many species of Metazoa has led the writer to undertake an analysis of the factors governing mitosis in these forms. Loeb ('12: 4) has called attention to the fact that the first attempt to reduce the phenomena characteristic of life to purely physico-chemical terms is found in the works of Lavoisier and Laplace ('80) which indicated that the heat produced in the body of a warm-blooded animal equalled that given off by a burning candle when the amounts of carbon dioxide produced in the two instances were equal. These results have been so much amplified by later workers that today no one doubts that the general processes having to do with the phenomena of metabolism are identical with the so-called purely physical and chemical reactions occurring outside the living body. In fact while metabolism, movement, and irritability are generally granted as probably due to the workings of the same principles that govern the inanimate realm the fourth of the vital properties, that of reproduction, is in great part still unexplained. No problem has offered more secure harbor for a final possibility of the presence of some supernatural force than has this one dealing with the processes of reproduction. The statement of Davenport ('08: 1); "The vital processes are chemical processes, taking place in a highly complex, very unstable, constantly changing substance, whose activities we call life," embodies the modern conception of the nature of life phenomena in general, but no attempt has been made to show the actual possibility of explaining all life processes on this basis.

An analysis of the possible factors determining or directing

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the course of nuclear and cell division is extremely difficult on account of problems involved in eliminating factors until but a single causal agent is operative. However, of the possible factors involved in the production of mitosis and of cleavage two groups are clearly recognizable, namely: (1) Environmental factors, and (2) Internal factors. Any change which occurs within the living organism must find explanation upon the basis of one of these two groups of factors or upon the basis of a combination of them. It is the purpose of this paper to show the relationship of these two groups of factors in the production of mitosis among those organisms which are made up of a fixed number of cells.

I. ENVIRONMENTAL FACTORS.

If environmental factors either caused or directly controlled the phenomena of mitosis the fact of cell constancy could not exist, for no two individuals, and more strongly no two groups of individuals even of the same species, develop under absolutely the same environmental conditions. Consequently if environmental factors were the limiting factors in mitosis no two individuals would of necessity contain the same number of cells. It is generally granted that the mitotic process may be accelerated or retarded through the application of purely external stimuli. At least in those organisms made up of a fixed number of somatic cells such an acceleration or retardation of the mitotic process could result in nothing beyond a modification of the normal *rate of the process* and could in no wise be considered as a direct factor in the determination of the *extent of the series* of mitotic divisions during the cleavage stages and in subsequent development. If the role of temperature, for instance, be examined as a possible controlling factor in the mitotic process it becomes apparent that if this alone and directly controlled the number of mitotic divisions through which the developing organism should pass there could be but slight possibility of any two individuals having identical numbers of somatic cells. For under conditions of nature no two individuals are at all times during their development under absolutely identical temperature relations. A similar variability of conditions for the development of different individuals exists in the case of almost all of the other environmental

factors which might be considered as directly influencing the process of mitosis.

Furthermore if environmental conditions could directly control and determine the mitotic process, cell division would continue indefinitely through the life of the organism as long as the external conditions remained favorable for it. Again the data brought from the field of cell-constancy show the impossibility of such factors being operative in a controlling manner. In the development of any organism or part of organism the powers of reproduction of most of the somatic cells are restricted to definite periods in the early stages of development, usually preceding the introduction of histological differentiation. Thus in the genus *Eorhynchus* the writer ('14: 280) has shown that in no instance did he find any adult worm displaying abnormal numbers of somatic nuclei or presenting any evidence whatever of further division of the somatic nuclei after the adult body form had been attained. These observations were upon over two hundred individuals collected during a period of four years at various localities and at various seasons of the year.

In conclusion, if the determination of the mitotic process were to find its explanation in terms of environmental factors, or to a continuous production of combinations of environmental factors during the process of development, then in every instance the number of mitotic divisions a fertilized egg would undergo would be a direct resultant of the complex of environmental factors operative during its process of development. At least in those forms with a high degree of cell constancy it seems obvious that purely environmental factors have but one relationship to the process of mitosis and that consists in the modifiability of the rate, either as an acceleration or as a retardation. In this respect purely environmental factors have the same general effect upon the process of mitosis as they exert upon purely physical and chemical reactions.

2. INTERNAL FACTORS.

Our incomplete knowledge of the finer structure of the cell, and of the nucleus in particular, make it impossible to associate the control of the mitotic process directly with any structure or

chemical bodies found in the cell. However on the basis of facts pointed out earlier in this paper it seems certain that since there is no possibility of environmental factors acting as the controlling element in mitosis the ultimate cause of the process must be sought within the cell. In this connection invaluable support is found in the field of experimental embryology. Morgan ('95, '01, and '03) and Driesch ('98 and '00) have both shown that in the embryos of echinoderms developed from isolated blastomeres of the two cell stage the number of cells present at any point in the development is approximately half of the number present in a normal embryo. Similarly from one of the blastomeres of the eight cell stage the gastrula is composed of only one eighth the number of cells found in the normal gastrula. Loeb ('06: 59) interprets these results as supporting the hypothesis of Sachs ('93 and '95) which regards the factors determining cleavage controlled by the ability of each nucleus to gather around itself and control a definite amount of protoplasm. Yet what determines the amount of protoplasm present in the developing individual? The cytoplasm is constantly being replaced through the processes of anabolism which experiments with enucleated cells have shown to be under the control of the nucleus. Consequently it seems that the view just stated comes not much short of being an argument in a circle. Does the amount of cytoplasm determine the number of nuclei that are to be formed or is the numerical relation of nuclei to cytoplasm a mutual one brought about not through the influence of either cytoplasm or of nucleus but through some fundamental factor which determines the number of nuclei and at the same time indirectly the amount of cytoplasm that is to be formed? The writer interprets the data of Morgan and of Driesch in an entirely different manner. If by the first division of the egg there are set apart two units, each of which has the possibility of developing into a given number of cells by the process of mitosis and this tendency is retained, even though the two units become separated, it seems logical to conclude that within the fertilized egg there are resident potencies which through the process of mitosis become divided between the two daughter nuclei of the first and then of each succeeding generation of cells.

As to the nature of this partition with each mitotic division two explanations present themselves. According to the simplest of these mitosis may be the result of the direct chemical activity of certain substances, present in the fertilized egg, which become used up in the mitotic process so that each cell of the two cell stage receives an equal amount of the substance present in the fertilized egg after the amount necessary for the first mitotic division has been eliminated. On this hypothesis with each succeeding mitotic division the materials resident in the developing embryo become partitioned and dissipated in the process of development. Thus if x equals the entire amount of the material for the execution of the mitotic process present in the fertilized egg, and a the amount required for the realization of the first mitotic division then each cell of the first cleavage would receive $(x - a)/2$. In this manner each succeeding division would reduce the amount of the material present until the amount apportioned to each cell would be less than the amount required for the execution of the mitotic process, thus bringing about an automatic check upon the course of the series of nuclear divisions. The following objection to such a hypothesis shows its weak point. Upon this basis each blastomere of the early stages would be required to produce the same number of cells, a supposition which the facts of cell lineage do not support.

The second explanation of the method of control over the number of divisions of the nucleus seems more natural and does not convey so much of the idea of predestination, in that it requires less emphasis upon the inherent qualities of the fertilized egg. According to this hypothesis mitosis is just as markedly a result of chemical processes going on within the egg as indicated above but the individual cells may in varying degrees retain the power of synthesizing the materials necessary to initiate and carry out the mitotic division of the nucleus. In the application of this explanation the check to the course of the nuclear divisions may come as the result of an accumulation of materials within the cell, probably as metabolic by products, which serve to retard and finally to prohibit the chemical activity incident to nuclear division. Thus at the end of any definite period of physiological activity the organism will be composed of a definite

number of cells and so upon attaining maturity will have a fixed number of somatic cells which are unable to divide farther on account of the presence of the inhibiting materials. It must be remembered that throughout this discussion principles are being laid down for the determination of the mitotic process in organisms or parts of organisms displaying cell constancy. The objection involving the variability in the number of cells arising from the early blastomeres, cited in connection with the discussion of the influence of environmental factors, finds no grounds here. In fact it lends its support to this second hypothesis. If the ultimate check to the mitotic process comes as the result of an accumulation of metabolic by products, then the *rate* of the nuclear division, which unquestionably may be influenced by environmental factors, would tend but to be directly proportional to the rate of the accumulation of the inhibiting elements, though the actual amount of the inhibitors necessary to terminate the series of mitotic divisions would remain the same. Evidently the accumulation of the inhibitors proceeds unequally in various tissues of the metazoan body. The degree of the differentiation of the cell and, in all probability connected with this, the nature of the cell membranes, determines the rate of the accumulation of the inhibiting factors.

The impossibility of explaining the phenomena of cell constancy on the basis of mitotic control by environmental factors and the facts from experimental embryology in their bearing upon the control of mitotic division by internal factors, lead to the evident conclusion that during the development of cell constant forms the mitotic process is controlled and determined from within the cell but its rate may be regulated by factors which are considered purely environmental.

CONCLUSIONS.

1. At least in those forms displaying a high degree of uniformity in the number and arrangement of their component cells and nuclei, environmental factors such as ordinarily influence physical and chemical changes play no direct part in the determination of the number of mitotic divisions of the somatic nuclei.
2. The only influence of normal environmental factors in these

forms consists in the modification of the rate of the process of mitosis.

3. The direct control of the mitotic process must be sought in the chemical activity going on within the cells of the developing individual.

4. Experimental evidence indicates that with each cleavage of an egg with determinate cleavage there is retained a definite relationship between the number of any given cleavage and the total number of cleavages that the embryo would undergo even in those cases where the blastomeres become isolated in the early stages of development.

5. The foregoing would indicate clearly that within the cells derived from the fertilized egg there are present factors or potencies which exert direct control over the number of mitotic divisions which shall ensue.

6. The fact that not all of the blastomeres of the early cleavages produce the same number of cells indicates that the number of cells produced must be controlled by conditions developing as the process of development progresses rather than by the partition and distribution of some definite materials present in the egg at a time prior to the first cleavage.

7. In tissues which retain the power of continued mitotic division, as for example in the formation of the germ cells and in tissues which have widely varying numbers of cells, the explanation of the inconstant nature of the numbers of cells produced may be sought in the acquisition of the power of eliminating from the cell those materials which in the course of the process of metabolism tend to accumulate and serve as inhibitors to the mitotic process.

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